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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,109	10/05/2007	John Colyer	9052-249	4321

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,109	COLYER ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *6,10 and 11* is/are withdrawn from consideration.

5)☒ Claim(s) *26 and 28* is/are allowed.

6)☒ Claim(s) *1-5,7-9,12-14,20-25,27 and 29* is/are rejected.

7)☒ Claim(s) *15-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/25/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species in the reply filed on 06/12/2009 is acknowledged.

2. During a telephone conversation on 6/30/2009, Applicants' representative, Shawna Lemon, indicated that the election of species in the reply filed on 06/12/2009 did not accurately reflect Applicants' intent, and that Applicants intended to elect species 'c' as set forth in the requirement for election/restriction mailed on 05/05/2009. The election is made with traverse. The traversal is on the ground(s) that the alleged non-linked species are indeed linked so as to form a single inventive concept under PCT Rule 13.1. Applicants argue that the alleged species of claim 10 (β-catenin), 11 (ADH), and 12 (PLB) all follow a single strategy to remove and replace individual protein targets, implemented by expressing a product comprising three modules: The first module allows the product to interact physically with the target (protein) molecule; the second module coordinates the rapid degradation of the target molecule; and the third module performs "the replacement function" acting like the original target molecule in all but at least one respect.

3. This is not found persuasive for the following reasons. As Applicants point out, the three species have different component parts fulfilling each of the three modules of the general strategy. The choice of components that will work for each target is necessarily based on the nature of the target. For example, the targeting module may be designed or derived from an interaction domain of a natural binding partner, a small drug-like molecule that binds the target, or a known enzyme substrate, among other possibilities. These would not be the same for each target; none is an obvious variant of another. Therefore each method of controlling target levels

would require a unique set of reagents, and the particulars of how to design the reagents to work together would be unique in each case. Therefore, each asserted target presents separate questions with regard to prior art and each asserted target raises different non-prior art issues under 35 U.S.C. 112, first paragraph. It is further noted that the present requirement is in agreement with the International Searching Authority, which did in fact find a lack of unity in the same claims presented in parent application PCT/GB05/00811. "In principle, each of the products mentioned in the claims represents a different invention" (PCT/ISA/206, page 2, of record).

The requirement is still deemed proper and is therefore made FINAL.

4. The elected species of product comprises a destruction module which acts indirectly on the target moiety and, therefore, it would not be used in the embodiment of the generic method recited in claim 6. Claims 6, 10, and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/12/2009.

5. Claims 1-5, 7-9, and 12-26 are under consideration.

Claim Objections

6. Applicant is advised that should claim 1 be found allowable, claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 4 recites the method according to claim 1 wherein the replacement module of the product is in the form of a modified form of the target moiety itself or is a functional unit which is capable of restoring normal metabolic activity of the cell into which the product has been introduced. However, this limitation is already present in claim 1(iii). There is no discernable difference in scope between claims 1 and 4.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 25 provides for the use of a vPLB nucleic acid, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

10. Claim 25 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

11. Claims 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 recites a product comprising a targeting module comprising a PLB target motif, a destruction module comprising absence of either or both lysine 3 and/or 27 so that ubiquitination cannot occur together with an N-terminal domain exhibiting a destabilizing N-terminal residue and a replacement module comprising a modified PLB sequence such that it is unable to inhibit Ca2+-pump activity. The metes and bounds of the "destruction module" are not clear. Reference is made to "lysine 3 and/or 27" but there is no identification of a defined sequence which comprises lysine 3 and/or 27. Thus, it is not clear upon which protein ubiquitination cannot occur or which protein has an N-terminal domain exhibiting a destabilising N-terminal residue.

12. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of "beneficial qualities" or others "considered detrimental" renders the claim vague and indefinite as these qualities may be matters of opinion or they may vary depending upon the circumstances.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of controlling levels/concentrations of phospholamban (PLB) comprising introducing into a cell a modified human PLB comprising an N-terminal domain in which the normal methionine at residue 1 has been replaced by an unstructured linker sequence and wherein either or both of lysine 3 and 27 is/are not expressed, and comprising a modified PLB sequence such that it is unable to inhibit Ca2+-pump activity, does not reasonably provide enablement for method of controlling levels/concentrations of any and all target moieties in a cell by introducing into a cell a targeting module, a destruction module and a replacement module. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

15. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been

described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The nature of the invention:* Although the broad language of claim 1 reads upon gene replacement by homologous recombination, the concept of the invention is the targeting and replacement of proteins in cells. The elected species employs a modified form of PLB to target, destroy, and replace PLB in cells.

b. *The state of the prior art and the predictability or lack thereof in the art:* The prior art provides examples of catalytic antagonists comprising a targeting moiety attached to an enzyme that degrades the molecule specifically bound by the targeting moiety (Davis et al, *ChemBioChem* 4:531-540 (2003), of record; see also US 20040170618, Abstract). Thus, with regard to direct acting destruction modules, such as proteinases, the instantly claimed methods differ from the prior art only by the inclusion of a replacement module into the product to be introduced into a cell. The prior art is silent, however, with respect to targeted destruction of proteins by indirect means. With regard to targeting, the propensity of PLB to oligomerize is well known in the art, to the extent that amino acids critical for oligomerization have been identified and the PLB

oligomerization domain can confer the ability to form complexes upon heterologous sequences (US Patent 6160088, FIG. 7; column 6, lines 7-31).

c. The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir.1991). The specification ([0086] in the published application) teaches a modified form of PLB protein, vPLB, is which has been designed to stimulate the catalytic removal of wild type PLB protein from the cell. The specification teaches that vPLB is able to achieve this effect because of two important features: Firstly, vPLB protein has a modified N-terminal domain in which the normal methionine at residue 1 has been replaced by an unstructured linker sequence, which would tend to render the protein unstable; and the replacement of lysine 3 and/or 27 (in the original PLB nucleic acid sequence of some species). Thus, although vPLB protein has a destabilising N-terminal residue, the absence of a lysine residue renders it stable as it does not possess a site for ubiquitin attachment (and therefore signal degradation). In cells, the formation of mixed oligomers of vPLB and wild type PLB appears to result in trans ubiquitination of wild type PLB and its subsequent removal from the ER (Examples 7-9). Thus, additional requirements are evident—the target must normally form oligomers, and the aforementioned modifications must not impair oligomer formation or otherwise impair activity. The specification provides no evidence or theory whereby susceptibility to ubiquitin-mediated proteolysis of a wild-type protein would be enhanced except by being brought into proximity with ubiquitin ligases that are unproductively interacting with the N-terminal arginine of the single species of vPLB

which was reduced to practice. The importance of the propensity of proteins to oligomerise is acknowledged in the specification at [0102-0104]. The specification asserts that replacing the N-terminal arginine of vPLB with a more stabilising residue would reduce the steady state level of wtPLB to some intermediate level [0106]. This hypothesis was not tested. It is further noted that vPLB is the only example in the specification wherein the destruction module acts indirectly on the target moiety and the destruction module comprises a mutation or deletion such that it alters degradation of the target moiety, as recited in claims 5 and 7.

d. The breadth of the claims and the quantity of experimentation needed: The broadest method claims recite the targeting, destruction, and replacement of any target moiety in a cell. Even if the targets are limited to proteins, as in claim 2, the number of potential targets is enormous. The instant claims are not limited to a strategy modeled upon vPLB or to targets that normally form dimers or oligomers. Even if the general strategy exemplified by vPLB were to be used, to make and use the invention the skilled artisan would first construct a modified form of a selected target which is unstable according to the N-rule but unable to be ubiquitinated. The modified target could only be useable in the claimed methods only if it localizes properly and can form mixed oligomers with the target protein. In the case of PLB, oligomer formation was previously known to be a characteristic feature of protein function. For other targets, the propensity to form oligomers of sufficient stability to achieve the desired effects is presently unknown. If the conditions of oligomer formation and localization are met, the modified protein might be able to cause trans-ubiquitination and selective destruction of the target,

as does vPLB. This, however, would still not be a useful method unless the replacement protein is further modified relative to the target so as to achieve some beneficially altered function—otherwise the method merely replaces a target with a functional equivalent. In the case of PLB, several such modifications were already known or suggested in the prior art. Such modifications would have to be discovered for each new protein the skilled artisan might attempt to target. Therefore, it would require undue experimentation for the skilled artisan to make and use the generic invention in its full scope.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1, 5, and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 20050130147, filed October 8, 2002. Claim 1 recites a method of controlling levels/concentrations of a target moiety comprising:(i) introducing into a cell a product comprising at least one of each of the following modules: a targeting module, a destruction module and a replacement module;(ii) targeting the target moiety with the targeting module of the product so as to bind them together or at least bring the target moiety into close

proximity with the product so that the destruction module can effect degradation of the target moiety; and (iii) replacing the target moiety with a replacement module, the replacement module either being a modified form of the target moiety itself or a functional unit which restores normal metabolic activity of the cell. This claim broadly reads on gene replacement by homologous recombination. In gene replacement, the target is a nucleic acid sequence within the cellular genome. The "targeting module", the "destruction module" and the "replacement module", are one in the same, being a modified form of the target which retains sufficient sequence identity with the target to "bring the target moiety into close proximity with the product". Homologous recombination results in both destruction (as in claim 5) of the target and its replacement. This is exemplified in Publication No. 20050130147, which teaches vectors for modifying a target DNA sequence contained in the genome of a cell. The vectors may comprise DNA sequences derived from the target so that the vector is capable of homologous recombination (see claim 81, for example) and, therefore, they are products as in instant claim 9.

18. Claim 13, 14, 20-25, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 20040121942, filed November 10, 2003. Claim 13 is drawn to isolated nucleic acid that encodes a modified or mutated form of PLB in which at least one lysine is not expressed. Dependent claim 14 specifies that either or both of lysine 3 and 27 is/are not expressed in the protein encoded by the vPLB nucleic acid. Claim 20 recites nucleic acid according to claim 13 further comprising any one or more of several mutations, including E2A and V49A. Claims 21-24 are drawn to the expressed protein, vectors, and a cell comprising

the recited nucleic acid from claim 13. These claims are anticipated by Publication No. 20040121942, which teaches recombinant adenoviruses for *in vivo* murine cardiac gene transfer to express point mutations of PLB, including V49A (Seq. ID. No. 2), E2A (Seq. ID. No. 3), a double point mutation of PLB, **K3E**/R14E (Seq. ID. No. 6) ([0047-0048], [0021]). Publication No. 20040121942 teaches therapeutic administration of the expressed proteins is to treat heart failure, as in claim 25 (as best it can be understood) and claim 29 (see abstract).

19. Claims 13, 14, and 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 20040215400, filed January 21, 2004. Publication 20040215400 discloses canine PLB and several modified, water-soluble derivatives of PLB, none of which have a lysine at position 27 (see FIG. 1). Publication 20040215400 further teaches expression of the encoding nucleic acids in cells [0093]. These disclosed nucleic acids represent modified or mutated forms of PLB in which either or both of lysine 3 and 27 is/are not expressed in the protein, as in claims 13 and 14; the disclosed vectors and cells meet the limitations of claims 21-24.

Conclusion

20. Claims 1-5, 7-9, 12-14, 20-25, 27, and 29 are rejected.

21. Claims 15-19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

22. Claims 26 and 28 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647